mutein thereof by infusion into one or more coronary vessels or into a peripheral vein in said human patient, said unit dose comprising from about .008 mg to 7.2 mg of a recombinant FGF-2 or an angiogenically active fragment or mutein thereof.

63. The method of claim 62, further comprising the step of administering 10 U/kg to 80 U/kg of heparin to said patient IV or IC about 0 to 30 minutes prior to administering said unit dose.

64. The method of claim 63, wherein FGF-2 has the amino acid sequence of the SEQ ID NO: 2.

65. A method for providing a human patient with relief from symptoms of angina comprising administering a single unit dose of a recombinant FGF-2 or an angiogenically active fragment or mutein thereof by infusion into one or more coronary vessels or into a peripheral vein in a human patient in need of relief from symptoms of angina, said unit dose comprising from about 0.008 mg to 7.2 mg of a recombinant FGF-2 or an angiogenically active fragment or mutein thereof.

66. The method of claim 65, further comprising the step of administering 10 U/kg to 80 U/kg of heparin to said patient IV or IC about 0 to 30 minutes prior to administering said unit dose.

67. The method of claim 66, wherein FGF-2 has the amino acid sequence of the SEQ ID NO: 2.--

REMARKS

Claims 1-9 have been canceled to expedite prosecution and expressly reserves the right to file a continuation application or take such other appropriate measures deemed necessary to protect the inventions in the canceled claims. Claims 10, 13, 15, 17, 22, 23, 26, 30, 33, and 35

have been amended. New claims 38-67 have been added. Support for the amendments and new claims resides throughout the specification. No new matter is added by way of claim amendment or presentation of new claims. Claims 10-67 are pending in the application.

Specifically, claims 10, 13, 15, 17, 22, 23, 26, 30, 33, and 35 have been amended to clarify that the single unit dose or therapeutically effective amount of a recombinant FGF-2 or an angiogenically active fragment or mutein thereof is administered into one or more coronary vessels or into a peripheral vein in a human patient receiving treatment in accordance with the methods of the invention.

The specification has been amended at page 1 to include a cross-reference paragraph reflecting the priority data as shown on the Substitute Declaration submitted concurrently herewith.

The Examiner's remarks in the Office Action are addressed below in the order set forth therein.

The Rejections of the Claims under 35 U.S.C. §102(b) Should Be Withdrawn

Claims 1-9 are rejected under 35 U.S.C. §102(b) as being anticipated by Baird *et al.*, U.S. Patent No. 5,155,214, based on an angiogenically active fragment. Claims 1-9 have been canceled to expedite prosecution. The Examiner is respectfully requested to withdraw this rejection.

Claims 1-15 are rejected under 35 U.S.C. §102(b) as being anticipated by Sellke *et al.* (1998) *Soc. Thoracic Surgeons* 65:1540-1544. Claims 1-9 have been cancelled. This rejection is respectfully traversed as applied to claims 10-15.

Sellke *et al.* disclose the treatment of coronary artery disease using heparin-alginate slow-release devices in patients undergoing coronary artery bypass grafting. During this surgical procedure, 10 heparin-alginate slow-release microcapsules (also referred to as beads), each containing either 1 ug or 10 ug of basic FGF (bFGF), were implanted in the epicardial fat or subepicardium (Abstract, paragraph 2, lines 8-10; page 1541, column 2, lines 20-23). The location of the epicardial fat or subepicardium tissue was in the "nongraftable myocardial region"

(page 1541, column 2, lines 23-24). The heparin-alginate beads were placed in "pockets through 2- to 3-mm slab incisions" (page 1541, column 2, lines24-25). Figure 1 shown on page 1541 shows that the heparin-alginate beads were placed within a tissue adjacent to a coronary vessel.

Independent claim 10 and claims 11-15 dependent thereon are directed to a method for treating a human patient for coronary artery disease. The method comprises administering a therapeutically effective amount of a recombinant FGF-2 or an angiogenically active fragment or mutein thereof into one or more coronary vessels or into a peripheral vein of a human patient in need of treatment for coronary artery disease. Sellke *et al.* do not teach administration of this growth factor or an angiogenically active fragment or mutein thereof into one or coronary vessels or into a peripheral vein to treat coronary artery disease. As the cited reference does not teach Applicant's invention, Applicant respectfully submits that the rejection under 35 U.S.C. §102(b) should be withdrawn.

The Rejection of the Claims under 35 U.S.C. §103(a) Should Be Withdrawn

Claims 1-37 are rejected under 103(a) as being unpatentable over Franco (U.S. Patent No. 4,378,347) in view of Uchida *et al.* (December 1995) *Amer. Heart J* 130(6):1182-1188 and Sellke *et al.* (1998) *Soc. Thoracic Surgeons* 65:1540-1544. Claims 1-9 have been canceled to expedite prosecution. This rejection is respectfully traversed as applied to claims 10-37.

Franco demonstrates myocardial injection of basic FGF (bFGF) in preclinical canine and feline models of acute myocardial infarction to obtain a beneficial reduction in infarct size. The reference suggests intravenous injection as a preferred mode of administration, but fails to demonstrate safety and/or efficacy in either animal model disclosed

Uchida *et al.* teach intrapericardial injection of 0.03 mg basic FGF (bFGF) plus heparin sulfate in a canine model of acute myocardial infarction. The route of administration is intrapericardial injection, not administration into one or more coronary arteries or into a peripheral vein. The investigators note that in their prior studies, intracoronary injection of bFGF in dogs resulted in a significant increase in the number of collateral vessels and subsequent salvage of the infarcted myocardium. However, the drawbacks of this type of therapy for acute myocardial infarction in a clinical setting are discussed. See column 2, lines 8-27. Thus, Uchida

et al. teach intrapericardial injection as a preferred method and teach away from intracoronary injection as a therapy for acute myocardial infarction.

Applicant respectfully notes that models of acute myocardial infarction are not predictive for a method of treatment for coronary artery disease, which represents a chronic ischemic condition as opposed to an acute ischemic event. Thus the beneficial results demonstrated in these two references with intrapericardial or myocardial injection cannot be extrapolated to treatment of coronary artery disease in accordance with the methods of the present invention.

As noted above, Sellke *et al.* teach administration of heparin-alginate slow-release beads comprising bFGF to the epicardial fat or subepicardial tissue surrounding the heart. This mode of administration represents an invasive surgical procedure where slow-release devices are implanted into tissue. This is a different route of delivery than that claimed by Applicant.

In contrast, the present invention is directed to administration of recombinant FGF-2 or angiogenically active fragment or mutein thereof into one or more coronary vessels or into a peripheral vein to promote angiogenesis in a patient suffering from coronary artery disease (CAD), to treat coronary artery disease (CAD, to treat myocardial infarction, and to provide relief from the symptoms of angina. The invention is based on a clinical trial with 66 participants at phase I. Applicant has clearly shown the prolonged therapeutic benefit of administering recombinant FGF-2 into one or more coronary vessels or into a peripheral vein of a patient having CAD. One mode of administering this growth factor is by infusion. The cited references alone or in combination do not teach or suggest administration of recombinant FGF-2 or angiogenically active fragment or mutein thereof directly into one or more coronary vessels or a peripheral vein to treat human patients in accordance with the methods of the present invention. As the cited references do not teach or suggest the claimed invention, Applicant's respectfully submit that this rejection of the claims should be withdrawn.

New Claims Presented

New claims 38-67 are directed to methods for treating a patient with CAD, for promoting angiogenesis in a patient in need of treatment for CAD, for treating symptoms of angina, and for treating myocardial infarction in a patient, where the methods comprise infusion of recombinant

FGF-2 or angiogenically active fragment or mutein thereof into one or more coronary vessels or into a peripheral vein. Support for the new claims resides throughout the specification as noted above. See, for example, page 22, lines 10-25. Applicants respectfully submit that the cited references do not teach or suggest this route of administration in humans in the manner recited in these claims.

Substitute Declaration

Applicant submits concurrently herewith a Substitute Declaration setting forth a claim for priority under 35 U.S.C. §119(e). The declaration recites as priority documents U.S. Application Serial Nos. 60/104,102 and 60/104,103, both filed October 13, 1998. Applicant respectfully requests the Examiner to enter this Substitute Declaration into the present application. It is requested that the application reflect a priority date of October 13, 1998. Applicant respectfully requests entry of the amendment to page 1 of the specification to include a specific cross-reference to these priority documents.

CONCLUSION

In view of the above amendments and remarks, Applicant submits that the rejections of the claims under 35 U.S.C. §102(b) and 103(a) are overcome. Applicant respectfully submits that this application is now in condition for allowance. Early notice to this effect is solicited.

If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject Application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of

this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

Leslie T. Henry

Leslie T. Henry
Registration No. 45,714

Customer No. 000826
ALSTON & BIRD LLP
Bank of America Plaza
101 South Tryon Street, Suite 4000
Charlotte, NC 28280-4000
Tel Raleigh Office (919) 420-2200
Fax Raleigh Office (919) 420-2260

CERTIFICATION OF FACSIMILE TRANSMISSION

I hereby certify that this paper is being facsimile transmitted to Examiner Hope Robinson at the Patent and Trademark Office at facsimile number (703) 308-0294, on June 4, 2001.

Polly P. Burton

Polly P. Burton

Version with Markings to Show Changes Made:

In the Specification

At page 1, after the title and before the Background of the Invention, please add the following cross-reference paragraph:

--This application claims the benefit of U.S. Provisional Application Serial Nos. 60/104,102, filed October 13, 1998, entitled "*Angiogenically Effective Unit Dose of FGF-2 and Method of Administering*," and 60/104,103, filed October 13, 1998, entitled *Angiogenically Effective Unit Dose of FGF and Method of Administering*," the contents of which are herein incorporated by reference in their entirety.--

In the Claims:

Please cancel claims 1-9.

Please amend claims 10, 13, 15, 17, 22, 23, 26, 30, 33, and 35 as follows:

10. (amended) A method for treating a human patient for coronary artery disease, comprising[,] administering a therapeutically effective amount of a recombinant FGF-2 or an angiogenically active fragment or mutein thereof [to]into one or more coronary vessels or [to]into a peripheral vein in a human patient in need of treatment for said coronary artery disease, said therapeutically effective amount being about 0.2 μg/kg to 48 μg/kg of patient weight.

13. (amended) The method of claim 12, wherein said therapeutically effective amount of a recombinant FGF-2 of SEQ ID NO: 2 or an angiogenically active fragment or mutein thereof is administered [to]into one or more coronary vessels.

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15. (amended) The method of claim 12 wherein said therapeutically effective amount of a recombinant FGF-2 of SEQ ID NO: 2 or said angiogenically active fragment or mutein thereof is administered [to]into a peripheral vein.

17. (amended) A method for treating a human patient for coronary artery disease, comprising[,] administering a single unit dose of a recombinant FGF-2 or an angiogenically active fragment or mutein thereof [to]into one or more coronary vessels or [to]into a peripheral vein in a human patient in need of treatment for coronary artery disease, said unit dose comprising from about .008 mg to 7.2 mg of a recombinant FGF-2 or an angiogenically active fragment or mutein thereof.

22. (amended) The method of claim 20, wherein said unit dose is administered [to]into one or more coronary arteries.

23. (amended) The method of claim 20, wherein said unit dose is administered [to]into a peripheral vein.

26. (amended) A method for inducing angiogenesis in a heart of a human patient, comprising[,] administering a single unit dose of a recombinant FGF-2 or an angiogenically active fragment or mutein thereof [to]into one or more coronary vessels or [to]into a peripheral vein in a human patient in need of treatment for coronary artery disease, said unit dose comprising from about .008 mg to 7.2 mg of a recombinant FGF-2 or an angiogenically active fragment or mutein thereof.

30. (amended) A method for [treating]preventing a myocardial infarction in a human patient, [for a myocardial infarction] comprising[,] administering a single unit dose of a recombinant FGF-2 or an angiogenically active fragment or mutein thereof [to]into one or more coronary vessels or [to]into a peripheral vein in said human patient, said unit dose comprising

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from about .008 mg to 7.2 mg of a recombinant FGF-2 or an angiogenically active fragment or mutein thereof.

33. (amended) The method of claim 30, wherein said unit dose is administered [to]into a peripheral vein.

35. (amended) A method for providing a human patient with relief from symptoms of angina, comprising administering a single unit dose of a recombinant FGF-2 or an angiogenically active fragment or mutein thereof [to]into one or more coronary vessels or [to]into a peripheral vein in a human patient in need of relief from symptoms of angina, said unit dose comprising from about 0.008 mg to 7.2 mg of a recombinant FGF-2 or an angiogenically active fragment or mutein thereof.